Nuovi criteri diagnostici per le varie forme di demenza

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THE DEMENTIAS

- Alzheimer’s Disease
- Lewy Bodies Dementia
- Frontotemporal Lobar degeneration
- Vascular Dementia
- Other diseases

[Image of a brain with different regions highlighted, including the frontal and temporal lobes, and labels for each condition]
Do we need “new” diagnostic criteria for dementias?
“Let's Rethink Alzheimer’s disease”

The Huffington Post, October 11, 2013
Clinical diagnosis of Alzheimer's disease

Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease
NINCDS-ADRA criteria for Alzheimer’s disease

*Neurology 1984;34:939–944*

**Probable AD**
- Deficits in two or more domains of cognition
- Progressive decline of memory and other cognitive functions
- Preserved consciousness
- Onset between ages 40 and 90
- Absence of systemic or other brain disease that could account for symptoms

**Possible AD**
- Atypical onset, presentation, or clinical course of dementia
- Presence of another illness capable of producing dementia

**Definite AD**
- Clinical criteria for probable AD
- Tissue diagnosis by autopsy or biopsy
The long way to Alzheimer

Brain Aging

"Brain" AD

MCI

AD

AAMI / ARCD

Cognitive Decline

Time (Years)

Moderate

Moderately Severe

Severe

Mild

Clinical AD

(Ferris, 4/03)
“New” Diagnostic Criteria for Dementias

Outline

• DSM 5 – A new Lexicon
• Alzheimer’s disease
• Frontotemporal Lobar Degeneration
• Dementia with Lewy Bodies
• Parkinson’s disease dementia
• Vascular dementia
DSM 5 – A NEW LEXICON

Neurocognitive Disorders - NCDs

• Major Neurocognitive disorder
• Minor Neurocognitive disorder
Etiology of Minor and Major NCDs

- Alzheimer’s disease
- Frontotemporal lobar degeneration
- Lewy body disease
- Vascular disease
- Traumatic brain injury
- Substance/medication-induced
- HIV infection
- Prion disease
- Parkinson’s disease
- Huntington’s disease
- Another medical condition
- Multiple etiologies
- Unspecified

“DSM-5 criteria have been developed in close consultation with the expert groups for each of the disease entities”
New criteria for Alzheimer’s disease
Rationale for New Criteria in AD

- The AD pathophysiological process likely starts years before cognitive changes and decades before onset of clinical dementia.
- Many patients whose cognition is not normal for age do not meet criteria for dementia.
- Other causes of dementia are more likely mistaken for AD.
- Genetics of AD are better understood.
- Biomarkers of AD are available in some centres.
- New criteria are needed for research.
- Specific treatments for the AD pathophysiological process are being developed; when these treatments are available it will be critical to know if patients have that process.
Current diagnostic algorithm for diagnosing and subtyping MCI

Cognitive complaint

Not normal for age
Not demented
Cognitive decline
Essentially normal functional activities

MCI

Memory impaired?

Yes

Amnesiac MCI

Memory impairment only?

Yes

Amnesiac MCI Single Domain

No

Amnesiac MCI Multiple Domain

No

Non-Amnesiac MCI

Single non-memory cognitive domain impaired?

Yes

Non-Amnesiac MCI Single Domain

No

Non-Amnesiac MCI Multiple Domain

MCI=mild cognitive impairment.

Biomarkers for conversion from MCI to AD
Biomarkers for Alzheimer’s disease

- Regional hypometabolism (FDG-PET)
- Microgliosis (e.g. PK11195 PET)
- Altered brain activation (fMRI)
- Inflammation / Oxidative Stress
  - ↑ CSF Tau and pTau
- Brain amyloid (e.g. PIB PET)
  - ↓ CSF Aβ42
- Brain atrophy (CT/MRI)

Graph showing:
- Neuronal integrity
- Amyloid plaques
- Neurofibrillary tangles

Legend:
- Non-demented
- Non-demented (Preclinical AD)
- Very mild AD (MCI)
- Mild AD
- Mod AD
- Sev AD

Graph illustrates the progression of biomarkers from non-demented to severe Alzheimer’s disease.
Research criteria for the diagnosis of Alzheimer’s disease: revising the NINCDS–ADRDA criteria


NIA-AA diagnostic guidelines for Alzheimer’s disease

*Alzheimer’s & Dementia 2011;7:257-292*

- Preclinical stages of Alzheimer’s disease
- Mild cognitive impairment due to Alzheimer’s disease
- Dementia due to Alzheimer’s disease
This is a newly defined stage of the disease reflecting current evidence that measureable biomarker changes in the brain may occur years before symptoms affecting memory, thinking or behavior can be detected by affected individuals or their physicians.
Preclinical Alzheimer’s disease

Hypothetical model of AD pathophysiological cascade

- Age Genetics
- Cerebrovascular risk factors
  Other age-related brain diseases

- Amyloid-β Accumulation
- Synaptic Dysfunction
  Glial Activation
  Tangle Formation
  Neuronal Death
- Cognitive Decline

- Brain and cognitive reserve
  ? Environmental factors
Staging of preclinical Alzheimer's disease

Stage 1
Asymptomatic amyloidosis
- High PET amyloid tracer retention
- Low CSF Aβ1-42

Stage 2
Amyloidosis + Neurodegeneration
- Neuronal dysfunction on FDG-PET/fMRI
- High CSF tau/p-tau
- Cortical thinning/ Hippocampal atrophy on sMRI

Stage 3
Amyloidosis + Neurodegeneration + Subtle Cognitive Decline
- Evidence of subtle change from baseline level of cognition
- Poor performance on more challenging cognitive tests
- Does not yet meet criteria for MCI

Mild Cognitive Impairment

Alzheimer's Disease
Addressing the ethical, policy, and social challenges of preclinical Alzheimer disease

ABSTRACT

Research suggests that Alzheimer disease (AD) pathophysiology begins prior to the clinical expression of the disease and that biomarker measures may provide direct evidence of this process. As a result, it may be possible to uncouple the diagnosis of AD from the clinical expression of the disease. The shifting boundaries between normal brain aging and disease present 3 challenges: 1) establishing guidelines for researchers and clinicians to safely and effectively communicate the diagnosis of preclinical AD, 2) setting up a process that effectively translates this diagnosis into practice and policy, and 3) adapting laws, regulations, and professional practices to the diagnosis of preclinical AD. The field of genetic testing for AD suggests how to balance a patient’s desire to know his or her risk of developing dementia with a clinician’s desire to mitigate the potential harms of that information. The development of diagnostic and treatment guidelines for other diseases of aging, such as cardiovascular disease, suggests the need for a National Alzheimer’s Education Program to develop policies and procedures to translate preclinical AD into both clinical practice and policy. Revisions are needed to laws, regulations, and professional practices governing driving, financial management and planning, and privacy and confidentiality. Neurology® 2011;77:1487-1493
In this stage, mild changes in memory and thinking are noticeable and can be measured on mental status tests, but are not severe enough to disrupt a person's day-to-day life.
Clinical and cognitive evaluation for MCI

Step 1

- Concern regarding a change in cognition: *History and observation.*
- Objective evidence of impairment in one of more areas of cognition (eg, memory, attention, language, visuospatial skills, executive function): *Neurocognitive testing.*
- Preservation of independence in functional abilities: *History, questionnaires.*
Clinical and cognitive evaluation for MCI

Step 2

- Examine aetiology of MCI: History, neurocognitive testing, imaging and laboratory studies.
- Define aetiology of MCI: AD, vascular, Lewy body, other degenerative disease, traumatic, depression, medical comorbidities, other.
- Provide evidence of longitudinal decline in cognition: History, serial neuropsychological testing.
In this stage, impairments in memory, thinking and behavior decrease a person's ability to function independently in everyday life.
Criteria for all-cause dementia:  

**Core clinical criteria**

A. Interfere with the ability to function at work or at usual activities;
B. Represents a decline from previous levels of functioning and performing;
C. Are not explained by delirium or major psychiatric disorders;
D. Cognitive impairment is detected and diagnosed by a combination of history taking and objective cognitive assessment;
E. The cognitive or behavioral impairment involves a minimum of two of the following: impaired ability to acquire and remember new information, impaired reasoning, impaired visuospatial abilities, impaired language functions, changes in personality and behaviour.
Probable AD dementia: *Core clinical criteria*

A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;
B. Clear-cut history of worsening of cognition by report or observation;
C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories:
   1. Amnestic presentation
   2. Nonamnestic presentation
D. The diagnosis of probable AD dementia should not be applied when there is evidence of another concurrent, active neurological disease, or a non neurological medical comorbidity.
New Diagnostic Criteria for AD: What do they really mean?

- There is a long preclinical period when AD pathology and brain damage are developing. Early and accurate diagnosis of the disease enable earlier intervention.

- Some people with MCI have cognitive decline due to underlying AD and some have other causes.

- Biomarkers can aid in the diagnosis of the different stages of AD.

- To develop effective therapies to delay or prevent cognitive decline and dementia, MCI due to AD and preclinical AD will need to be a target for future clinical trials.
Frontotemporal Lobar Degeneration and the new criteria for behavioural variant FTD
Frontotemporal Dementia: The Problem of Polysemy

- Pick’s disease
- Pick-complex disorder
- Progressive subcortical gliosis
- Dementia lacking specific pathology
- Frontal dementia of the non-Alzheimer type
- Frontotemporal dementia (FTD)
- Frontotemporal lobar degeneration (FTLD)
Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia.

Brain 2011;134:2456-2477
I. NEURODEGENERATIVE DISEASE
In order to meet criteria for any bvFTD diagnosis, the patient must show a progressive deterioration of behaviour and/or cognition by observation or history. This core symptom aims to distinguish bvFTD from acute medical events or stable conditions such as long-standing psychiatric disease.

II. POSSIBLE bvFTD
The diagnosis of possible bvFTD is based on personality, social comportment and cognitive features that discriminate bvFTD from other conditions. While it is important to interpret diagnostic features of a case in the clinical context, ratings of behavioural features can be difficult and potentially open to observer bias. As such, we encourage ratings that are based on overt behaviours, as opposed to inferences about a patient's cognitive or emotional state.
Three of the following behavioural or cognitive symptoms (A–F) must be present:

A. Early Behavioural Disinhibition
B. Early Apathy or Inertia
C. Early Loss of Sympathy or Empathy
D. Early Perseverative, Stereotyped or Compulsive/Ritualistic Behaviour
E. Hyperorality and Dietary Changes
F. Neuropsychological Profile: Executive/Generation Deficits With Relative Sparing of Memory and Visuospatial Functions
III. PROBABLE bvFTD
The diagnosis of probable bvFTD is based on functional and imaging findings that discriminate this disorder from other dementias, psychiatric disorders and non-degenerative conditions such as the phenocopy syndrome.

IV. bvFTD With DEFINITE FTLD PATHOLOGY
This conclusive diagnostic category is based on the presence of a known pathogenic mutation or histopathological evidence of FTLD (on biopsy or autopsy).
A

Accounted by non-degenerative / medical

Accounted by psychiatric dx

Biomarkers strongly indicative of AD
(exclusion criteria for Probable bvFTD)

% cases

% Total sample (n=176)
% Common sample (n=137)

B

Abrupt onset with ictal events

Head trauma related to onset

Early, severe amnesia

Spatial disorientation

Logoclonic festinant speech

Myoclonus

Corticospinal weakness

Cerebellar ataxia

Choreoatetosis

Imaging: posterior / multifocal

Lab tests: brain inv / inflammatory

% cases

% 1998 criteria sample (n=152)
% common sample (n=137)
OBJECTIVE: To evaluate the interrater reliability of the new International Behavioural Variant FTD Criteria Consortium (FTDC) criteria for behavioral variant frontotemporal dementia (bvFTD).

RESULTS: The mean κ value for diagnostic agreement was 0.81 for possible bvFTD and 0.82 for probable bvFTD ("almost perfect agreement"). Interrater reliability for 4 of the 6 core features had "substantial" agreement (behavioral disinhibition, perseverative/compulsive, sympathy/empathy, hyperorality; κ = 0.61-0.80), whereas 2 had "moderate" agreement (apathy/inertia, neuropsychological; κ = 0.41-0.6). Clinician years of experience did not significantly influence rater accuracy.

CONCLUSIONS: The FTDC criteria show promise for improving the diagnostic accuracy and reliability of clinicians and researchers. As disease-altering therapies are developed, accurate differential diagnosis between bvFTD and other neurodegenerative diseases will become increasingly important.
Dementia with Lewy Bodies
Dementia with Lewy Bodies

History of Diagnostic Criteria

- 1996 - DLB characterized (1st Consensus conference)
  McKeith et al, *Neurology*, 1996

- 1999 - report from 2nd consensus conference on DLB.
  McKeith et al, *Neurology*, 1999

- 2005 - report from 3rd consensus conference on DLB.
  McKeith et al, *Neurology*, 2005

- 2006 – 4th consensus conference on DLB held.
  Publication pending
Dementia with Lewy Bodies

**Diagnostic criteria**

- Presence of dementia
- Impairment often maximal in attention/concentration and visuospatial functioning
- Core features*
  - Recurrent fully formed visual hallucinations
  - Fluctuations in cognition or arousal
  - Spontaneous parkinsonism
  - * 2+ present for clinically probable DLB,
  - 1 present for clinically possible DLB

* 2+ present for clinically probable DLB,
  - 1 present for clinically possible DLB
Dementia with Lewy Bodies

Diagnostic criteria

- **Suggestive features:**
  - REM sleep behavior disorder (which may precede onset of dementia by several years)
  - Severe neuroleptic sensitivity
  - Abnormal (low uptake) in basal ganglia on SPECT dopamine transporter scan or abnormal (low uptake) MIBG myocardial scintigraphy
Dementia with Lewy Bodies

DAT scan

Normal

DLB
Dementia with Lewy Bodies

MIBG
Dementia with Lewy Bodies

Diagnostic criteria

• **Supportive features:**
  – Repeated falls and syncope (fainting).
  – Transient, unexplained loss of consciousness.
  – Autonomic dysfunction.
  – Hallucinations of other modalities.
  – Visuospatial abnormalities like depth perception, object orientation, directional sense and illusions.
  – Other psychiatric disturbances like systematized delusions, aggression and depression.
Parkinson’s Disease Dementia
“...involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a funning pace, the senses and the intellects uninjured.”
PDD: History

• Scientific efforts during the past two decades have led to improved understanding of the biology of and diagnostic consensus criteria for dementia and mild cognitive impairment in Parkinson’s disease and to a licensed drug treatment for dementia in Parkinson’s disease.

• However, many key questions about treatment, care, and diagnosis remain unanswered.
Prevalence and Incidence of PD


In Italy, the crude prevalence per 100,000 population was 371.5 for all types of parkinsonism and 257.2 for Parkinson's disease.

Incidence of PD by age and gender

Prevalence of PDD

Demographic Model for Prevalence of PDD by Duration of PD and Gender

Impact and Burden of PDD

• Dementia symptoms of PD are the greatest contributors to caregiver distress.
• They are often more distressing than motor symptoms.
• Increases relative risk of skilled placement by more than threefold.
• Risk of mortality increases when PD patients develop dementia.
PDD: convergence of α-synuclein tau and amyloid-β pathologies

Nature Reviews Neuroscience
I. Core features

1. Diagnosis of Parkinson’s disease according to Queen Square Brain Bank criteria

2. A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson’s disease and diagnosed by history, clinical, and mental examination, defined as:
   - Impairment in more than one cognitive domain
   - Representing a decline from premorbid level
   - Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms
Litvan I, et al.

Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines.

MCI IN PARKINSON’S DISEASE

I. Inclusion criteria

Diagnosis of Parkinson’s disease as based on the UK PD Brain Bank Criteria

Gradual decline, in the context of established PD, in cognitive ability reported by either the patient or informant, or observed by the clinician

Cognitive deficits on either formal neuropsychological testing or a scale of global cognitive abilities

Cognitive deficits are not sufficient to interfere significantly with functional independence, although subtle difficulties on complex functional tasks may be present
Vascular Dementia
Cognitive deficits and cerebral vascular disease: the new standards.

- Vascular cognitive impairment (VCI) includes vascular dementia (VaD), vascular mild cognitive impairment (VaMCI) and mixed dementia.

- To improve the characterization of VCI and to refine its diagnostic criteria, an international group has elaborated a new standardized evaluation battery of clinical, cognitive, behavioral and neuroradiological data which now constitutes the reference battery (Stroke, 2010).

- Criteria of VCI are based on the demonstration of a cognitive disorder by neuropsychological testing and either history of clinical stroke or presence of vascular lesion by neuroimaging suggestive of a link between cognitive impairment and vascular disease.
Take-home messages

- New clinical criteria for the diagnosis of preclinical AD, MCI, MCI due to AD, AD, bvFTD, PDD, and VCI are now available.
- The pathophysiological mechanisms of these diseases are still not completely understood.
- There is a long preclinical period when pathological mechanisms are developing.
- It is necessary to diagnose and treat these diseases in the early stages or even before they become symptomatic.
- Preventive strategies may be useful in delaying disease onset.
Thank you for your attention